sives (1.8 ± 1.2 pg/ml) compared to normotensives (1.3 ± 0.9, p < 0.05), indicating persistent inflammation. The association between FMD and t-PA and TNF-α remained significant after adjustments for cardiovascular risk factors. Thus, inflammatory and prothrombotic mediators play a role in the pathogenesis of atherosclerosis over and above the effects of classic risk factors. Antihypertensive therapy alone may be insufficient to improve endothelial dysfunction in hypertensives with high plasma levels of inflammatory markers. Additional therapy to target inflammation may be necessary to improve endothelial function and to prevent progression of coronary atherosclerosis in high-risk hypertensives with subclinical inflammations.

1011-96 **Lipid Profile of Hypertensive Patients With Hyperlipidemia and Coronary Artery Disease After Treatment With Nebivolol: A Beta-Blocker With Enhanced Nitric Oxide Release**

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Background: Antihypertensive therapy should ideally reduce LDL- and increase HDL-levels in hypertensive patients prone for cardiovascular disease. In the present multi-center observational study, the effects of nebivolol, a selective beta1-receptor blocking agent which enhances endothelial nitric oxide (NO) release, were investigated in hypertensive patients with Hyperlipidemia (HLP) and coronary artery disease (CAD).
Methods: 8682 patients were included, average age 56.3±12.0 years, 53.8% males. Of these 3084 (35.5%) had HLP, 377 (4.3%) had additionally CAD. Besides systolic and diastolic blood pressure (BP), serum lipid values were measured before and after an average 59.7 days of treatment with nebivolol. According to the treating physicians co-medication and dietary habits remained unchanged.
Results: The systolic and diastolic BP reduced in mean by 26.6±14.4 and 13.6±9.0 mmHg respectively. The LDL-levels decreased significantly from 156.7±42.5 to 145.4±37.9 mg/dl (p<0,05). The HDL-levels increased significantly on the other hand under treatment from 46.8±19.1 to 48.8±16.3 mg/dl (p<0,05).
Conclusions: Treatment with nebivolol lead to an increase in HDL-levels and a decrease in LDL-levels. The findings can only partly be explained by the BP lowering effect of nebivolol. A possible enhanced endothelial NO release, which has been shown for nebivolol previously, could explain the lipid lowering effects of this drug. Further studies are required to underline these results.

1011-96A **Effects of Lipid-Lowering Therapy With Fibrates on Endothelial Function in Patients With Type 2 Diabetes Mellitus**

Hideki Watanabe, Kunio Nakagawa, Masaaki Kakihana, *KINU Medical Association Hospital, Mitsukaido, Japan, Ibaraki Prefectural University of Health Sciences, Ami, Japan.*

Dyslipidemia characterized by elevated triglyceride (TG) and reduced HDL-cholesterol (HDL-C) has been reported in patients with type 2 diabetes mellitus (DM). To evaluate effects of fibrates on endothelial functio, twenty-four type 2 diabetic patients with elevated TG (TG>150 mg/dL) were randomized to receive either fibrates (bezafibrate: B group, n=7; fenofibrate: F group, n=5) or placebo (n=12). By using ultrasound with a 7.5-MHz transducer, the brachial artery diameter was measured at rest and during reactive hyperemia (flow-mediated dilatation, FMD), and before and after 0.3 mg of sublingual nitroglycerin (nitroglycerin-induced dilatation, NID). These measurements were performed in 12-hour overnight fasting condition at baseline and after 3 months of the treatment. At baseline, there was no difference in lipid parameters, fasting glucose level, HbA1c, brachial artery diameters, %FMD (%increase in diameter during hyperemia), and %NID (%increase in diameter after NTG) among three groups. After 3 months, triglyceride and LDL-C levels were significantly decreased, and HDL-C level was significantly increased in the fibrates groups (TG: B group, -38%, F group -45%; LDL-C: B group, -11%, F group -14%; HDL-C: B group, +18%, F group +19%). %FMD was improved after 3 months of treatment with fibrates. On the other hand, %NID, fasting glucose level and HbA1c did not change after 3 months. Conclusion: Lipid-lowering therapy with fibrates might restore endothelial function in patients with type 2 DM.

		Baseline	3M
%FMD (%)	Bezafibrate	3.3 ± 1.1	7.8 ± 1.8 *†
	Fenofibrate	3.3 ± 0.4	8.3 ± 1.8 *†
	Placebo	3.2 ± 0.6	3.4 ± 1.1
%NID (%)	Bezafibrate	18.5 ± 1.9	18.1 ± 1.8
	Fenofibrate	18.0 ± 0.5	18.2 ± 1.2
	Placebo	18.4 ± 1.4	18.1 ± 1.5

mean ± SD
* p<0.01 vs Baseline
† p<0.01 vs Placebo

POSTER SESSION

1031 Endothelin, Heat Shock Proteins, and Cytokines in Atrial Septal Defect: Basic Studies

Sunday, March 17, 2002, Noon-2:00 p.m.
Georgia World Congress Center, Hall G
Presentation Hour: Noon-1:00 p.m.

1031-82 **Sensitivity to Endothelin Is Increased in the Endothelial Dysfunction of Epicardial Coronary Arteries in Left Ventricular Hypertrophy in Swine**

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Background: We have recently demonstrated that NO-mediated endothelium-dependent relaxations are impaired in left ventricular hypertrophy (LVH) after 60 days of pressure overload produced by aortic stenosis. Whether increased endothelium-dependent contractions contributes to this endothelial dysfunction is unknown.
Objective: The aim of this project was to assess the sensitivity of endothelium-dependent vasoconstrictor ET-1 and endothelium-independent serotonin (5-HT) on the vascular smooth muscle of coronary arteries of swine submitted to 60 days of aortic banding. The plasmatic levels of the NO2-/NO3- ratio was measured to assess the production of NO in this model.
Methods: Banding was performed through a left thoracotomy using umbilical tapes for 60 days period. A minimal gradient of 15 mmHg was created by an aortic banding 3 cm above the coronary ostia. Development of LVH was documented by serial echocardiograms. Endothelium-dependent and independent contractions to ET-1 and 5-HT were studied by constructing dose-response curves in organ chamber experiments to evaluate the increase sensitivity to vasoconstriction (in the presence of indomethacin and propranolol). The plasma level of NO2-/NO3- was measured with a NO analyzer.
Results: 60 days after aortic banding, there is an increase in endothelium-dependent contractions to ET-1 (P<0.05) and to 5-HT (P<0.05) compared to the control group. There is also a decrease in the NO2-/NO3- ratio 60 days after aortic stenosis (P<0.05).
Conclusion: With the development of LVH secondary to aortic stenosis, the sensitivity of the vascular smooth muscle to ET-1 is increased as well as the sensitivity to 5-HT in coronary arteries. Decreased production of NO, could contribute to the increased tendency of epicardial coronary arteries to vasoconstriction. The dual mechanisms of endothelial dysfunction of decreased production of endothelial NO and increased sensitivity to vasoconstrictors may impair myocardial function by rendering cardiac muscle more susceptible to ischemic injury. Pharmacological therapy should be both aimed at increasing endothelial NO and inhibiting ET-1 to improve endothelial function of coronary arteries in LVH.

1031-83 **Chronic Selective Endothelin A Receptor Antagonism Preserves Myocardial Perfusion in Experimental Hypercholesterolemia**

Piero O. Bonetti, Patricia J. Best, Martin Rodriguez-Porcel, David R. Holmes, Jr., Lilach O. Lerman, Amir Lerman, *Division of Cardiovascular Diseases and Division of Hypertension, Mayo Clinic, Rochester, Minnesota.*

Experimental hypercholesterolemia (HC) leads to coronary endothelial dysfunction, endothelin activation, increased vascular permeability, and attenuation of the myocardial perfusion (MP) response to increased myocardial demand. Chronic administration of endothelin A receptor (ETA) antagonists preserves coronary endothelial function in HC. However, whether this translates into preservation of MP is still unknown. Thus, the current study was designed to test the hypothesis that chronic ETA antagonism would preserve MP in HC.
Methods: Pigs were randomized to 3 experimental groups: normal diet (N; n=7), high cholesterol diet (HC; n=7) and HC diet plus ABT-627, a selective ETA antagonist (HC+ABT-627; n=7) for 12 weeks. Electron beam computed tomography of the heart was performed before and during intravenous infusion of adenosine to calculate MP (ml/min/g myocardial tissue) and microvascular permeability index (PI; arbitrary units).
Results: LDL-cholesterol was significantly and similarly increased in the HC and HC+ABT-627 group compared to N. As shown in the table, ABT-627 improved MP and preserved PI during adenosine infusion in HC.
Conclusion: The current study demonstrates that chronic ETA antagonism with ABT-627 preserves MP response to increased myocardial demand in HC in association with preservation of microvascular permeability. This suggests a role for the endogenous endothelin system in the regulation of MP in pathophysiological states associated with endothelial dysfunction.

Myocardial perfusion and microvascular permeability index at baseline and in response to adenosine

	N	HC	HC+ABT-627
MP baseline	0.90+/-0.1	0.95+/-0.1	1.03+/-0.1
MP adenosine	1.30+/-0.1*	0.92+/-0.1	1.33+/-0.1*
% Change of MP to adenosine	+48+/-7	-2+/-4†	+29+/-6
PI baseline	1.54+/-0.1	1.34+/-0.2	1.62+/-0.1
PI adenosine	1.73+/-0.2	2.26+/-0.2*	1.82+/-0.1
% Change of PI to adenosine	+11+/-5	+78+/-13†	+15+/-7

* p < 0.001 vs baseline
† p < 0.005 vs N and/or HC+S